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Impact of Cytoreductive Surgery and HIPEC on Intraoperative Gastrointestinal Wall Thickness and Patient Outcomes

MICHELLE ZHIYUN CHEN[1,2], DANIEL L. CHAN[1,2,3], MOHAMMAD S. ALSHAHRANI[1], KHALED ALTOUKHI[1], NAYEF ALZAHRANI[1,2,4] and DAVID L. MORRIS[1,2]

[1]*Department of Surgery, St. George Hospital, Kogarah, NSW, Australia;*
[2]*Faculty of Medicine, The University of New South Wales, Sydney, NSW, Australia;*
[3]*Faculty of Medicine, Western Sydney University, Sydney, NSW, Australia;*
[4]*College of Medicine, Imam Muhammad ibn Saud Islamic University, Riyadh, Kingdom of Saudi Arabia*

Abstract. *Background: Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) is associated with significant postoperative ileus (POI). This study examined intraoperative gastrointestinal wall thickness (GWT) and its association with patient outcomes. Patients and Methods: A prospective study of patients undergoing CRS and HIPEC. Proximal and distal small intestine GWT, before and after HIPEC were recorded. Results: Thirty-four patients (mean age=56.1 years, 61.8% female) were recruited. After HIPEC, the mean proximal (4.5 vs. 3.0 mm, p=0.03) and distal (4.3 vs. 3.4 mm, p<0.01) GWT were increased. Increased GWT was associated with prolonged operative time (10 vs. 8.5 h, p=0.03) and total length of stay (35.71 vs. 21.25 days, p=0.02). Postoperative ileus occurred in 23.5% of patients but differences between GWT groups did not reach significance (28.6% vs. 20%, p=0.56). Conclusion: GWT increased significantly during CRS and HIPEC and is reflective of tissue trauma and oedema. This was associated with prolonged operative time, total length of stay and post-operative ileus.*

Cytoreductive surgery (CRS) for management of regionally advanced intra-abdominal malignancy can achieve improved disease-free and overall survival (1). Traditionally considered incurable, peritoneal dissemination of malignancy is increasingly managed with CRS and heated intraperitoneal chemotherapy (HIPEC) for a range of both primary and recurrent disease (2-4). Reflecting the magnitude of the intervention, the survival benefit of CRS and HIPEC is weighed against high perioperative morbidity. Although a learning curve of surgical experience is recognised, even in experienced high-volume centres, mortality of around 4% and morbidity about 42% are reported (5, 6).

The morbidity of delay in return to gastrointestinal function and postoperative ileus in the context of major abdominal CRS is recognised. Postoperative ileus leads to nausea, vomiting, bloating and reduced tolerance to oral intake, which negatively affects outcomes, including hospital length of stay (LOS) (7, 8). The addition of HIPEC to CRS likely has a compounding effect on bowel trauma and gastrointestinal function. Postoperative ileus following CRS and HIPEC has been reported in 15-54% of patients and accounts for about 15% of early hospital re-admissions (9-11).

Although the exact cellular and molecular mechanisms of postoperative ileus remain unclear, there is a significant overlap with patients being critically unwell (12). Radiological measurement of gastrointestinal wall thickness (GWT) is used as a predictor of ischaemia in intestinal obstruction (13). GWT secondary to oedema has been associated with being critically unwell, judicious fluid resuscitation and is associated with delayed intestinal transit in animal models (12-14). There is a paucity of literature on intraoperative measurements of GWT and associations with postoperative ileus or other patient outcomes. Our study aimed to examine the association between intraoperative GWT measurements and patient outcomes in patient undergoing CRS and HIPEC.

Patients and Methods

A prospective study was conducted in 2018 at a major referral centre for CRS and HIPEC with two experience surgeons and a high case volume. A power calculation for sample size was not performed due

Correspondence to: Professor David L. Morris, Hepatobiliary and Surgical Oncology Unit, Department of Surgery, St George Hospital, Level 3 Pitney Building, Gray Street, Kogarah, Sydney, NSW 2217, Australia. Tel.: +61 291132590, Fax: +61 291133997, e-mail: David.Morris@unsw.edu.au

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to the pilot nature of this study and the lack of evidence in the literature to guide such a calculation. Patients were recruited preoperatively. Intraoperative measurements of the GWT at the duodenojejunal flexure (DJ) and terminal ileum (TI) were taken with calipers. Measurements were taken after entry into the abdominal cavity before HIPEC, and after HIPEC prior to abdominal closure and recorded on the operation report. Of note, our centre routinely performs gastrointestinal anastomosis, when required, after HIPEC. The primary outcome was the effect of CRS and HIPEC on GWT. Secondary outcome was assessment of outcomes when comparing patients with increased versus non-increased GWT. Additional clinical data including patient demographics, disease characteristics (type, primary *vs*. second CRS), intraoperative findings (peritoneal carcinomatosis index (PCI), enterotomy or serosal injury, HIPEC time, operative time) and postoperative outcomes (first defaecation, anastomotic leak, postoperative ileus, total and intensive care LOS) were retrieved through electronic medical records.

Recovery of gastrointestinal motility was measured by day of first defaecation. POI was diagnosed when the first defaecation was on postoperative day 6 or later, consistent with literature (11). Increased GWT was defined as an increase in of 3 mm or more of the combined DJ and TI wall thickness. Eligibility criteria included: Adult patients (>18 years of age); with peritoneal carcinomatosis of any primary pathology; undergoing CRS and HIPEC; consent to participate. Exclusion criteria included: Undergoing debulking surgery only; no HIPEC. This study was approved by the Institutional Ethics Review Board.

Descriptive statistics were tabulated and are reported as number (%) and mean±standard deviation (range). Differences in means were assessed with independent and paired *t*-tests. Differences in categorical variables by Pearson Chi-squared test where appropriate. A value of $p<0.05$ was considered statistically significant. Statistical analysis was conducted with SPSS Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Thirty-four patients were recruited in this study. The average age was 56.1±13.6 (range=27-81) years. The majority were female (61.8%). The American Society of Anesthesiologists (ASA) status of patients was 3 or 4 in 88.2%. The most frequent malignancy was colorectal cancer (35.3%). The mean total PCI was 19±12.5 (range=2-39), and mean small bowel PCI was 3±2.8 (range=0-9). Of these patients, 28 (82.4%) had a completeness of cytoreduction score (CC) of CC0 and the remaining six patients (17.6%) had CC1 (Table I).

The mean pre-HIPEC DJ wall thickness was less than that post-HIPEC (3.0 *vs*. 4.5 mm, $p=0.03$). The mean pre-HIPEC TI wall thickness was also less than that post-HIPEC (3.4 *vs*. 4.3 mm, $p<0.01$). Increased GWT in DJ and TI was present in 14 (41.2%) patients. This increase in GWT was not significantly different amongst the males and females ($p=0.33$) in our study. Small intestine PCI or total PCI also did not significantly affect increase in GWT ($p=0.34$; $p=0.97$). Increase in GWT was not associated with the type of surgery ($p=0.67$), duration of HIPEC ($p=0.47$) or intraoperative serosal injury or enterotomy ($p=0.26$).

Overall, eight patients (23.5%) had postoperative ileus. When comparing patients with and without increased combined GWT, frequency of postoperative ileus was increased but did not reach significance (28.6 *vs*. 20%, $p=0.347$). Both operative time (10 *vs*. 8.5 h, $p=0.03$) and total LOS (35.71 *vs*. 21.25 days, $p=0.02$) were significantly longer in those who had increased GWT. Intensive care LOS was also longer but did not reach statistical significance (6.14±4.4 *vs*. 4.00±2.2 days, $p=0.07$). There was no difference in return to gastrointestinal function in those with and without increased combined GWT (4.6±2.1 *vs*. 4.9±1.9 days, $p=0.77$). There was no anastomotic leak or mortality in our series.

Discussion

CRS and HIPEC are two parts of a treatment modality for peritoneal carcinomatosis. First described in 1980, CRS with perioperative intraperitoneal chemotherapy has been the standard of care for all cases of mucinous appendiceal neoplasms with peritoneal dissemination, without distant metastases, for almost two decades (15, 16). In a 2006 consensus statement, it was recognised that standardization of CRS and HIPEC technique significantly improved survival of Stage IV colon cancer (17). As a reflection of procedural complexity, there is a wide range of reported perioperative morbidity (40-80%) and mortality (3-20%) (18). Improvements with appropriate patient selection, high-volume surgeon and centre experience, standardization of CRS and HIPEC and in perioperative management continue to develop. Morbidity and mortality rates are now comparable with similar high-risk surgical oncology procedures, such as oesophagectomy, major hepatectomy and pancreaticoduodenectomy (19, 20).

Nonetheless, recovery after such a major operation is often associated with delayed recovery of gastrointestinal motility. Postoperative ileus accounts for a large proportion of morbidity and readmissions in patients treated with CRS and HIPEC (10). Our postoperative ileus rate of 23.5% reflects the broader experience. A multitude of factors contribute to the development of postoperative ileus, including surgical manipulation, bowel oedema, anastomotic leakage, intraperitoneal sepsis, pre-operative septic state, high cancer burden and lung disease (21, 22). The exact pathophysiology of postoperative ileus is unclear but direct trauma and fluid resuscitation leads to inflammation of the *muscularis propria* and reduced gastrointestinal motility (14, 23).

Both DJ and TI GWT were significantly increased after CRS and HIPEC. Not previously defined, we used an approximate 50% increase of GWT (increase ≥3 mm of combined DJ and TI thickness) as the cut-off, given the expected clinical implications of such oedema. Although the primary outcome, postoperative ileus, was increased in patients with increased GWT compared to those without, this

Table I. *Patient demographics*.

	Overall	Increased GWT	No increase in GWT	*p*-Value
Age, years				
Mean±SD	56.21±13.56	59.4±11.8	54±14.5	
Gender, n (%)				
Female	21 (61.8%)	10 (71.4%)	11 (55%)	0.33
Male	13 (38.2%)	4 (28.6%)	9 (45%)	
ASA score, n (%)				
1	0 (0%)	0 (0%)	0 (0%)	0.77
2	4 (11.8%)	1 (7.1%)	3 (15.0%)	
3	28 (82.4%)	12 (80%)	16 (85.7%)	
4	2 (5.9%)	1 (7.1%)	1 (5%)	
Cancer type, n (%)				
Appendiceal	15 (44.1%)	7 (50%)	8 (40%)	NA
Colorectal	12 (35.3%)	1 (7.1%)	11 (55%)	
Mesothelioma	2 (5.9%)	2 (14.3%)	0 (0%)	
Ovarian	3 (8.0%)	2 (14.3%)	1 (5%)	
Small bowel	1 (2.9%)	1 (7.1%)	0 (0%)	
Ovarian+appendiceal	1 (2.9%)	1 (7.1%)	0 (0%)	
PCI, mean±SD				
Total	19±12.47	23±12.6	16±11.8	0.97
Small bowel	3±2.78	4±2.7	3±2.8	0.34
CC, n (%)				
0	28 (82.4%)	11 (78.6%)	17 (85%)	0.628
1	6 (17.6%)	3 (21.4%)	3 (15%)	
2	0 (0%)	0 (0%)	0 (0%)	

ASA: American Society of Anesthesiologists, PCI: peritoneal carcinomatosis index, CC: completeness of cytoreduction, GWT: gastrointestinal wall thickness, NA: not applicable.

did not reach statistical significance (28.6 *vs*. 20%, $p=0.347$). However, total LOS was prolonged in these patients (35.71 *vs*. 21.25 days, $p=0.02$). The cause for this prolonged LOS is unclear, given the logical concern of delayed return to gastrointestinal function (4.6 *vs*. 4.9 days, $p=0.77$) and postoperative ileus rates were not significantly different. We hypothesize that this could be due to small patient numbers in our study leading to type I error.

Prolonged operative time (10 *vs*. 8.5 h, $p=0.03$) was also noted in patients with increased GWT, without significant differences in disease characteristics, including disease extent (PCI), difficultly of clearance (CC score) and primary *vs*. second CRS. Whether this increased operative time was a product of the difficulty of gastrointestinal tissue manipulation or a reflection of the cause of prolonged fluid resuscitation is unknown. A meta-analysis recently concluded that a prolonged operative time >2 h increases the likelihood of complications and every 30 min of additional operative time increases this by 14% (24).

GWT was also found in patients with higher small bowel PCI and total PCI ($p=0.0336$; $p=0.97$). This is a reflection of increased technical difficulty of CRS but, interestingly, it was not statistically significant. Given the magnitude of CRS and HIPEC, the operative times in our groups well exceeded those of this meta-analysis, although it should be noted that the duration of HIPEC was not significantly different between groups. Perhaps the absolute application of HIPEC, rather than its duration, contributes to increased GWT; however, this was outside of the scope of our study design. Likely, there is a combination of both cause and effect of prolonged operative time on increased GWT in our study.

The limitations of our study were the small patient numbers, subjective intraoperative measurements and measure of gastrointestinal motility recovery. The small patient number reflects the pilot nature of the study, being the first to describe a quantitative intraoperative increase in GWT. Intraoperative GWT measurements are by their nature, subjective. All measurements were taken with the same caliper instrument but timing of measurements was not standardized. We considered this when defining increased GWT to account for possible inter-observer variability. Our definition of recovery of gastrointestinal motility was the day of first postoperative defaecation. Given a recent study that employed both gastric emptying and colonic transit studies, the combination of tolerance of solid diet in addition to day of first defecation may be a better outcome measure (8).

Intraoperative GWT measurement is a novel measure of gastrointestinal tissue trauma. Although anecdotal evidence

is available, to our knowledge, this is the first report of quantitative intraoperative GWT findings in the literature. The combination of CRS and HIPEC was associated with significantly increased GWT and prolonged operative time and LOS in our study. The relationship between causative factors, increased GWT and patient outcomes warrant further investigation with larger prospective series.

Conflicts of Interest

None.

Authors' Contributions

Study design: D. Morris, N. Alzahrani, M. Alsharani; Intraoperative data collection: M. Chen, D. Chan, M. Alsharani, K. Altoukhi; Data analysis and interpretation: M. Chen, D. Chan; Drafting of article: M. Chen, D. Chan, K. Altoukhi; Final approval of version to be published: D. Morris, N. Alzahrani.

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